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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,957	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-21,30 and 33-38* is/are pending in the application.

4a) Of the above claim(s) *36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 14-21, 30, 33-35, 37, and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :November 3, 2006 and May 17, 2007.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed August 14, 2007.

New claims 37 and 38 are acknowledged. Claims 1, 20, 30, and 35 have been amended.

Claims 1, 14-21, 30, and 33-38 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1, 14-21, 30, 33-35, 37, and 38) in the reply filed on August 14, 2007 is acknowledged. The traversal is on the ground(s) that no undue burden exists to examine all of the herein presented claims in their entirety. In particular, Applicants argue that the inventions of Groups I and II recite closely related inventions based on the same inventive concept, i.e., a chemically modified double stranded nucleic acid molecule and a method of using such a molecule. As such, Applicants argue that art of the same class will be used to examine all of the claims of the instant application. Applicant's traversal has been fully considered, but is not found persuasive because, while the Examiner agrees that the inventions of Groups I and II are drawn to a chemically modified double stranded nucleic acid molecule and a method of using such a molecule, respectively, as discussed in the Restriction Requirement mailed May 14, 2007, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product, see MPEP §

806.05(h). For example, the chemically modified nucleic acid molecule that is complementary to a human vascular endothelial growth factor (VEGF) RNA of Group I can be used in a materially different process such as a hybridization probe in a method of identifying human VEGF expression *in situ*, which is a materially different process than the method of inhibiting the expression of human vascular endothelial growth factor (VEGF), comprising administering a chemically modified double stranded nucleic acid molecule that is complementary to a human VEGF RNA of Group II. As discussed in MPEP § 806.05(h), absent a convincing argument that the alternative use suggested by the Examiner cannot be accomplished, the fact that the product can be used in a materially different process of using that product renders the product and process of use distinct. In this light, the Examiner has considered Applicant's traversal and has decided that the inventions of the two Groups represent divergent subject matter. Because these inventions are independent or distinct for this reason, there would be a serious burden on the Examiner if restriction were not required because the inventions require a different field of search (see MPEP 808.02). Therefore, restriction for examination purposes as indicated is proper.

Claim 36 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 14, 2007.

Applicant is reminded that the examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a

product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note

that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1, 14-21, 30, 33-35, 37, and 38 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statements filed November 3, 2006 and May 17, 2007 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements, and signed copies are enclosed herewith.

Priority

It is noted that the instant claims are currently drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications.

The Examiner acknowledges that the instant application claims priority to PCT/US03/05022, which claims the benefit of provisional application 60/363,124, filed March 11, 2002.

The instant application has been afforded priority to January 26, 2004, which is the filing date of the instant application because support for the invention as now claimed cannot be found in parent applications PCT/US03/05022 or provisional application 60/363,124.

Response to Arguments

Applicants filed a Request for Continued Examination on May 1, 2007. In this Request, Applicants argued that the instant invention is entitled to a priority date of at least March 11, 2002, which is the filing date of the 60/363,124 application.

The Examiner has considered this argument, but has not found it persuasive because support for the invention as claimed cannot be found in the 60/363,124 application. Specifically, support for a chemically modified nucleic acid molecule complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications cannot be found.

In summary, Applicant does not receive the benefit of the earlier filed application 60/363/124 because the prior application does not provide adequate support for the

claims of the instant application and thus Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. Applicants contend that the instant invention is entitled to a priority date of at least March 11, 2002, which is the filing date of the 60/363,124 application. While the provisional application 60/363,124 provides support for a chemically modified nucleic acid molecule complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, the provisional application 60/363,124 does not provide support for wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications. If Applicants believe that they are entitled to an earlier priority date, then Applicant must point, with particularity, to where such support can be found in the specification of the prior application.

******

As discussed *supra*, the claims are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474. The Examiner would like to note that provisional application 60/363,124 has support for SEQ ID NO:474. It is noted that Applicants contend that **SEQ ID NO:474 is the sequence of GenBank Accession Number NM_003376** (see Applicant's Remarks filed May 1, 2007 at page 8, first full paragraph). It is further noted that GenBank

Accession Number NM_003376 was submitted and made of record on the IDS filed July 22, 2004. Incidentally, the nucleotide sequence of GenBank Accession Number NM_003376 submitted in the IDS filed July 22, 2004 is 1723 nucleotides in length, however, SEQ ID NO:474 as recited in the sequence listing of the instant application is only 649 nucleotides in length. Furthermore, GenBank Accession Number NM_003376 consecutively comprises only the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]). Given the fact that GenBank Accession Number NM_003376 as submitted on Applicant's IDS filed July 22, 2004 and SEQ ID NO:474 of the instant invention appear to be different sequences, with very different lengths, it does not appear that Provisional Application 60/363,124 has support for a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 as instantly claimed. In this regard, the instant application has been afforded priority to January 26, 2004, which is the filing date of the instant application because it is the Examiner's position that **SEQ ID NO:474 is not the sequence of GenBank Accession Number NM_003376**.

Response to Arguments

In Applicant's Request for Continued Examination, filed on May 1, 2007, Applicants argue that GenBank Accession Number NM_003376 has different published versions. For example, Applicants argue that the version of GenBank Accession Number NM_003376 disclosed in provisional application 60/363,124, i.e., the version available as of March 11, 2002, was 649 nucleotides. Applicants further argue that the GenBank Accession Number NM_003376 sequence published on November 1, 2000 was also 649 nucleotides in length. Applicants respectfully submit that the instant application is entitled to a priority date of at least March 11, 2002, which is the filing date of the 60/363,124 application, since the version of GenBank Accession Number NM_003376, at the time of the priority application 60/363,124, was 649 nucleotides.

The Examiner has considered this argument, but has not found it persuasive because while GenBank Accession Number NM_003376 may have different published versions, the version submitted and made of record on Applicant's IDS filed July 22, 2004 is the only version that the Examiner is relying on. If Applicant intended for a different version to be considered by the Examiner, then that version should have been submitted and made of record before the submission made on July 22, 2004.

In sum, the evidence of record recites GenBank Accession Number NM_003376 as having 1723 nucleotides in length (see GenBank Accession Number NM_003376 submitted on Applicant's IDS filed July 22, 2004). However, Applicants now claim that GenBank Accession Number NM_003376 has different published versions, one being 649 nucleotides in length as represented by SEQ ID NO:474 of the instant invention.

Applicants argue that the version of GenBank Accession Number NM_003376 disclosed in the priority 60/363,124 application, i.e., the version available as of March 11, 2002, has 649 nucleotides. The Examiner is concluding that the sequence of GenBank Accession Number NM_003376 [of record] (1723 nucleotides in length), and SEQ ID NO:474 (649 nucleotides in length) of the instant invention are different sequences with very different lengths. Furthermore, GenBank Accession Number NM_003376 consecutively comprises only the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]). In light of these facts, SEQ ID NO:474 of the instant invention does not represent GenBank Accession Number NM_003376 as Applicants contend. Therefore, provisional application 60/363,124 does not have support for a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474.

Specification

The amendment filed May 1, 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the

Amendment filed May 1, 2007, Applicants have amended all the pending claims to be directed to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474. The sequence of SEQ ID NO:474 appears to be new matter.

As discussed *supra*, the evidence of record recites GenBank Accession Number NM_003376 as having 1723 nucleotides in length (see GenBank Accession Number NM_003376 submitted on Applicant's IDS filed July 22, 2004). **However, Applicants contend that SEQ ID NO:474 represents GenBank NM_003376** (see Applicant's Remarks filed May 1, 2007 at page 10, forth paragraph). It is noted that SEQ ID NO:474 of the instant invention is only 649 nucleotides in length. Furthermore, GenBank Accession Number NM_003376 consecutively comprises only the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]). In light of these facts, SEQ ID NO:474 of the instant invention does not represent GenBank Accession Number NM_003376 as Applicants contend. As discussed *supra*, the Examiner is concluding that the sequence of GenBank Accession Number NM_003376 [of record] (1723 nucleotides in length), and SEQ ID NO:474 (649 nucleotides in length) of the instant invention are different sequences with very different lengths. Thus, **SEQ ID NO:474 does not represents GenBank NM_003376.**

Therefore, claims drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 are new matter.

Response to Arguments

In Applicant's Request for Continued Examination, filed on May 1, 2007, Applicants acknowledge that GenBank NM_003376 was submitted and made of record on the information disclosure statement filed July 22, 2004. Applicants also acknowledge that GenBank NM_003376, submitted and made of record on the information disclosure statement filed July 22, 2004, has 1723 nucleotides in length. Applicants argue that the nucleotide sequence of GenBank NM_003376 that was published at the time of filing of the priority application (provisional application 60/363,124) has 649 nucleotides. Applicants however argue that SEQ ID NO:474 is not new matter because at the time of filing of the priority application (provisional application 60/363,124), the sequence of GenBank Accession Number NM_003376 had 649 nucleotides

Applicants argument has been considered but is not found persuasive because, as discussed *supra*, the Examiner is relying on the sequence of GenBank Accession Number NM_003376 that has been made of record - that sequence being 1723 nucleotides in length (see Document No. 160 on the IDS filed July 22, 2004). Furthermore, GenBank Accession Number NM_003376 consecutively comprises only the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2

Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]). In light of these facts, SEQ ID NO:474 of the instant invention does not represent GenBank Accession Number NM_003376 since SEQ ID NO:474 is only 649 nucleotides in length. Therefore, the sequence of GenBank Accession Number NM_003376 [of record] (1723 nucleotides in length), and SEQ ID NO:474 of the instant invention (649 nucleotides in length) are different sequences with very different lengths. Thus, claims drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 are new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14-21, 30, 33-35, 37, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474. The sequence of SEQ ID NO:474 appears to be new matter.

As discussed *supra*, the evidence of record recites GenBank Accession Number NM_003376 as having 1723 nucleotides in length (see GenBank Accession Number NM_003376 submitted on Applicant's IDS filed July 22, 2004). **However, Applicants contend that SEQ ID NO:474 represents GenBank NM_003376** (see Applicant's Remarks filed May 1, 2007 at page 10, forth paragraph). It is noted that SEQ ID NO:474 of the instant invention is only 649 nucleotides in length. Furthermore, GenBank Accession Number NM_003376 consecutively comprises only the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]). In light of these facts, SEQ ID NO:474 of the instant invention does not represent GenBank Accession Number NM_003376 as Applicants contend. As discussed *supra*, the Examiner is concluding that the sequence of GenBank Accession Number NM_003376 [of record] (1723 nucleotides in length), and SEQ ID NO:474 (649

nucleotides in length) of the instant invention are different sequences with very different lengths. Thus, **SEQ ID NO:474 does not represents GenBank NM_003376.** Therefore, claims drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 are new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

In Applicant's Request for Continued Examination, filed on May 1, 2007, Applicants argue that **SEQ ID NO:474 and GenBank Accession Number NM_003376 are the same sequence** (see Applicant's Remarks filed May 1, 2007 at page 12, first paragraph). Applicants argue that the nucleotide sequence of GenBank Accession Number NM_003376 published at the time of filing of the priority application (November 1, 2000) has 649 nucleotides and is the same sequence as SEQ ID NO:474, which is 649 nucleotides.

Applicant's arguments have been considered, but are not found persuasive because as discussed *supra*, the Examiner is relying on the sequence of GenBank Accession Number NM_003376 that has been made of record - that sequence being 1723 nucleotides in length (see Document No. 160 on the IDS filed July 22, 2004). In light of this fact, **SEQ ID NO:474 and GenBank Accession Number NM_003376 are not the same sequence.** Thus, claims drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense

strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 are new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 14-21, 30, 33-35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number NM_003376 (Applicant's Document No. 160 on Applicant's information disclosure statement filed July 22, 2004), in view of Reich et al. (Molecular Vision, 2003 Vol. 9:210-216, Applicant's Document No. 256 on the information disclosure statement filed July 22, 2004), Elbashir et al.

(EMBO Journal, 2001 Vol. 20:6877-6888, Applicant's Document No. 114 on the information disclosure statement filed July 22, 2004), Matulic-Adamic et al. (US Patent No. 5,998,203), and Parrish et al. (Applicant's Document No. 246 on the information disclosure statement filed July 22, 2004).

Applicant is reminded that the instant application has been afforded priority to the filing date of the instant application, which is January 26, 2004. For further explanation, see the discussion above under the heading "Priority".

The claims are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-deoxy-2'fluoro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a

terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified nucleic acid molecule.

GenBank Accession Number NM_003376 teaches a sequence of a human vascular endothelial growth factor (VEGF). It is noted that GenBank Accession Number NM_003376 consecutively comprises the first 438 nucleotides of SEQ ID NO:474 of the instant invention (see Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376 [submitted and made of record in the Office Action mailed November 1, 2006]).

GenBank Accession Number NM_003376 does not teach a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, wherein each strand is 18 to 27 nucleotides in length, wherein about 50% to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-deoxy-2'fluoro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or

both, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified nucleic acid molecule.

Reich et al. teach specific siRNA nucleic acid inhibitors of human VEGF gene expression. Reich et al. teach siRNA targeting human VEGF effectively inhibits ocular neovascularization in a mouse model (see Abstract). Reich et al. teach siRNA duplexes consisting of a sense and antisense strand targeted to human VEGF (see page 211, first column, first paragraph). Reich et al. also teach RNA interference significantly diminishes levels of human VEGF protein expression (see Figure 3).

Elbashir et al. teach RNA interference (RNAi) is a newly discovered pathway of inhibiting gene expression by using an antisense-like mechanism. Specifically, Elbashir et al. teach short interfering RNAs (siRNAs) as mediators of RNAi and inhibitors of gene expression. Detailed protocols and methods are provided for designing, preparing, testing, and using siRNA to silence/inhibit expression of virtually any known gene. Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). For example, Elbashir et al. teach complete substitution (e.g. 100%) of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-

deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate extensive (50% to 100%) substitutions/chemical modifications to a siRNA molecule as discussed below.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures (see Abstract). The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications (see Figure 5). One or both strands comprise modifications.

Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the RNA interference process (see Summary).

It would have been obvious *prima facie* to one of ordinary skill in the art at the time the invention was made to make a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 using the sequence taught by GenBank Accession Number NM_003376, the motivation of Reich et al., and following the methods of Elbashir et al., Matulic-Adamic et al., Parrish et al. It would have been obvious to have the siRNA comprised in a pharmaceutically acceptable carrier or diluent using the teachings and motivation of Reich et al.

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate at least one 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate or deoxyabasic nucleotide modifications into the chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474, since Elbashir et al., Matulic-Adamic et al., and Parrish et al. taught various modifications have been incorporated into double stranded nucleic acids to facilitate uptake of the nucleotide. It would have been obvious to incorporate a terminal cap moiety on one of the ends of the sense strand since Matulic-Adamic et al. taught such modifications protect the nucleic acid from exonuclease degradation. It would have

been obvious to incorporate a phosphorothioate internucleotide linkage at the 3' end of the antisense strand or a terminal phosphate group at 5'-end of the antisense strand since either Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. teach such modifications protein the nucleic acid from nuclease attack.

One would have been motivated to incorporate at least one 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications into a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 since these modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid, as taught by Elbashir et al., Matulic-Adamic et al., Parrish et al. It was well known in the art at the time of filing to incorporate two or more modifications, including 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications, into oligonucleotides, as evidenced by Elbashir et al., Matulic-Adamic et al., and Parrish et al. Elbashir et al. had demonstrated both 2'-deoxy and 2'-O-methyl modifications of double stranded oligonucleotides at the time the invention was made. Matulic-Adamic et al. taught double stranded oligonucleotides comprising more than one specific type of modification. Additionally, Parrish et al. teach various modifications to double stranded duplexes and teach that different modifications are tolerated at different locations of the duplex. Elbashir et al. and Parrish et al. demonstrate the routine nature of testing various chemical modifications for optimization and stabilization of a double stranded duplex. The cited art demonstrates that the specific modifications were extensively

described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a double stranded nucleic acid molecule in order to optimize delivery of the nucleic acid. One of skill in the art would be motivated to have the siRNA comprised in a pharmaceutically acceptable carrier or diluent to facilitate its delivery *in vitro* or *in vivo.*

There would be a reasonable expectation of success to apply each of the claimed modifications to the nucleic acid molecules taught by Reich et al. because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. Modifications of chemically modified nucleic acid molecule comprising a sense strand and an antisense strand was known to be successful in the art at the time the invention was made and therefore one would reasonably expect for such modifications to benefit the chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence comprising SEQ ID NO:474 as instantly claimed.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Response to Arguments

In Applicant's Request for Continued Examination, filed on May 1, 2007, Applicants argue that none of the reference, alone or in combination, make obvious the

presently claimed double stranded nucleic acid constructs because the cited references do not teach or suggest all of the claim elements. For example, Applicants argue that none of the references teach or suggest a siRNA molecule in which about 50% to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications. This argument has been fully considered, but is not found persuasive because firstly, the claims are not drawn to siRNA molecules, *per se*. Instead, the claims are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand, which read on ribozymes, long dsRNAs, and other double stranded nucleic acid constructs of the like. Secondly, the reference of Elbashir et al. teach a siRNA molecule in which about 50% to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications. For example, Elbashir et al. teach complete substitution (e.g. 100%) of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate extensive substitutions/chemical modifications to a siRNA to determine overall RNAi activity.

Applicants next argue that none of the references teach or suggest a siRNA molecule in which one or more of the purine nucleotides present in one or both strands are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands are 2'-deoxy-2-'fluoro pyrimidine nucleotides. This argument has been fully considered, but is not found persuasive because firstly, Applicant is reminded that the claims are not drawn to siRNA *per se*, but instead are drawn broadly to include, for example, ribozymes. Secondly, both Elbashir et al. and Matulic-Adamic et al. teach chemically modified nucleic acid molecules comprising a sense strand and an antisense strand in which one or more of the purine nucleotides present in one or both strands are 2'-O-methyl purine nucleotides, while Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications.

Applicants next argue that Matulic-Adamic et al. is directed to ribozyme technology and fails to teach or suggest a chemically modified siRNA molecule of Applicant's invention. This argument has been fully considered, but is not found persuasive because Applicant is reminded that the claims are drawn to chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human VEGF nucleotide sequence, and thus reads on ribozymes, for example.

Applicants next argue that Elbashir teaches away from the use of highly modified siRNA constructs, such as 2'-deoxy and 2'-O-methyl modified constructs since

extensive substitution with 2'-deoxy and 2'-O-methyl modifications abolishes RNAi. This argument has been fully considered, but is not found persuasive because, as discussed *supra*, while Elbashir et al. teach that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, the instant claims do not recite any functional language. Therefore, the skilled artisan would have been motivated to incorporate highly modified substitutions/chemical modifications to a siRNA to determine overall RNAi activity. In view of this evidence, Elbashir do not teach away from the use of highly modified siRNA constructs, but instead, motivates the skilled artisan to incorporate extensive modifications to determine overall RNAi activity.

Applicants next argue that Parrish teaches long dsRNA molecules, and not chemically synthesized short interfering RNA molecules of Applicant's invention. This argument has been considered, but is not found persuasive because, as discussed *supra*, the claims are drawn to chemically modified nucleic acid molecules comprising a sense strand and an antisense strand. The breadth of the claims include, for example, ribozymes, long dsRNAs, and other nucleic acid constructs of the like.

Applicant next argues that antisense and ribozyme art, such as the disclosure of Matulic-Adamic is not analogous art to siRNA technology and should not be the basis for an obviousness rejection. This argument has been considered, but is not found persuasive because, as discussed *supra*, the claims are not drawn to siRNA, but include, for example, ribozyme nucleic acid molecules. Furthermore, contrary to Applicant's argument, antisense and ribozyme art are analogous to siRNA technology

since independently antisense, ribozyme, and siRNA all have the same general purpose - to function as inhibitors of nucleic acid gene expression. This is evidenced by the post-filing reference of Scanlon, K. (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420) where the author categorizes antisense, ribozyme, and siRNA as anti-gene molecules, which use anti-gene technology to illicit gene silencing effects (see entire article). Furthermore, Applicant is reminded that it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. Therefore, it would be obvious to substitute a siRNA with a ribozyme, and vice versa.

Applicants finally argue that, at the time the invention was made, it was thought that additional chemical modifications to siRNAs were unnecessary for effective RNAi activity, thus providing no reasonable expectation of success. Applicants point the Examiner to Elbashir II (Methods, 2002 Vol. 26:199-213) where specific instructions are detailed for designing and carrying out an RNAi experiment. This argument has been fully considered, but is not found persuasive because, first, there would be a reasonable expectation of success to make an extensively modified siRNA in view of the teachings of Elbashir et al. As discussed *supra*, Elbashir et al. teach that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues. While complete substitution may have abolished RNAi activity, Applicant is reminded that the instant claims do not recite any functional language. Therefore, the skilled artisan would have been motivated and expected success in incorporating extensive substitutions/chemical modifications to a siRNA to determine overall RNAi activity. In

view of this evidence, Elbashir do not teach away from the use of highly modified siRNA constructs, but instead, motivates the skilled artisan to incorporate extensive modifications to determine overall RNAi activity. Second, the claims are broadly drawn to include, for example, ribozymes and long dsRNAs. Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. Therefore, there would be a reasonable expectation of success to apply each of the claimed modifications to the double stranded nucleic acid structures of Matulic-Adamic et al. because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice.

The evidence of records shows that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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tcg
September 2, 2007

/Terra Cotta Gibbs/